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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> :  A61K 45/06		A1	(11) International Publication Number: <b>WO 99/21585</b>  (43) International Publication Date: 6 May 1999 (06.05.99)		
(21) International Application Number: PCT/IB98/01789		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).			
(22) International Filing Date: 19 October 1998 (19.10.98)					
(30) Priority Data: 97/13426 27 October 1997 (27.10.97) FR					
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(54) Title: PHARMACEUTICAL COMBINATION OF A CYCLOOXYGENASE-2 INHIBITOR AND ACETAMINOPHEN OR AN OPIATE					
(57) Abstract					
<p>The object of the present invention is a pharmaceutical composition, characterized in that it comprises as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from acetaminophen and the opiates.</p>					

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PHARMACEUTICAL COMBINATION OF A CYCLOOXYGENASE-2 INHIBITOR AND ACETAMINOPHEN OR AN OPIATE

The object of the present invention is a novel pharmaceutical combination having application notably in the treatment of pain and inflammatory phenomena.

5 More specifically, the invention relates to a pharmaceutical composition which comprises, as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from acetaminophen and the opiates.

Selective cyclooxygenase-2 (COX-2) inhibitors constitute a novel class of non-steroid analgesic and anti-inflammatory agents. Such compounds have been described  
10 for example in the documents WO 94/15932, WO 96/03388 by GD Searle, WO 95/00501 by Merck & Frosst Canada Inc., WO 95/18799, WO 96/08482 by Merck & Co., and FR 2747123, FR 2747124 by the Applicant.

Amongst the particularly preferred compounds which have been described in the state of the art,

15 - 5-bromo-2-[4-fluorophenyl]-3[4-methanesulphonylphenyl]thiophen, known under the code name of DuP 697 ;  
- 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulphonamide known under the designation Celecoxib ;  
- (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]-  
20 dihydrofuran-2-one known under the code name UP 454-21,  
may be notably cited.

Generally, these compounds also possess anti-inflammatory and analgesic activities, the latter being demonstrated in various experimental inflammatory pain models.

25 However, it is known that the selective cyclooxygenase-2 inhibitors are inactive or not very active in the non-inflammatory acute pain tests. Thus, *Gans et al.*, J. Pharm. Exp. Ther. 1990 ; (254) : 180-187 have demonstrated that the product DuP 697 mentioned above is inactive in the phenylbenzoquinone test in the mouse.

Acetaminophen, or paracetamol, N-(4-hydroxyphenyl)acetamide, or 4'-hydroxyacetanilide, is a well-tolerated medicament which possesses an analgesic and

anti-pyretic activity and is commonly used in the symptomatic treatment of painful and febrile ailments at daily doses in the order of 500 to 3000 mg.

The opiate or morpholinic compounds are powerful centrally-acting analgesics indicated in the treatment of moderate to severe pain and are able to induce  
5 dependence and addiction in certain circumstances.

It has been discovered, and this constitutes the basis of the present invention, that the combination of a cyclooxygenase-2 inhibitor and a compound selected from paracetamol and the opiates possesses a significant analgesic effect at doses at which each one of the products constituting this combination is inactive or not very active.

10 The beneficial effect of the combination in accordance with the present invention has been demonstrated both in inflammatory pain models and in acute pain models, and particularly in the phenylbenzoquinone (PBQ) test and the heated plate test in the mouse. The results obtained have shown that this combination possesses an analgesic activity greater than that of each one of these constituent products used alone at the  
15 same dose.

The potentiation effect thus demonstrated makes the use of low doses of each one of the constituent products of the combination possible by thus limiting their possible side effects.

Moreover, this combination enables treating pain of very varied origin in a  
20 larger number of patients.

Advantageously, the pharmaceutical combination in accordance with the present invention will be in a form suitable for an administration:

- via the oral route, such as simple or coated tablets, capsules or granules, for example;
- 25 - via the rectal route, such as suppositories for example
- via the parenteral route, such as injectable preparations for example
- via the ocular route, such as eye lotions or ophthalmic solutions for example;
- via the transdermal route

- via the nasal route, such as aerosols and sprays for example; or
- via the auricular route, such as drops for example.

- Such a composition can be prepared, according to the methods known *per se*, by incorporating the active principle, consisting of the above-mentioned combination,
- 5 with excipients usually used such as talc, gum arabic, lactose, starch, magnesium stearate, polyvidone, cellulose derivatives, cocoa butter, semi-synthetic glycerides, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, glycols, wetting agents, dispersing agents or emulsifiers, silicone gels, certain polymers or co-polymers, preservatives, aromas and coloring agents.
- 10 In general, any compound having a cyclooxygenase-2 inhibiting activity can be used within the context of the present invention, preferably, diaryl methylidenetetrahydrofuran derivatives will be used such as those described in the applications FR 2747123 and FR 2747124 of the Applicant which are incorporated herein by reference.
- 15 A particularly preferred compound is (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]dihydrofuran-2-one known under the code name of UP 454-21.

- The opiates which can be used within the context of the present invention may be of a different nature : powerful opiates, the top one of which is morphine, 20 which can treat severe pain, such as morphine itself or oxycodone, or weak opiates, which can treat pain of moderate intensity, such as codeine or dextropropoxyphen.

Derivatives having a powerful central analgesic effect, oxycodone in particular, will be more particularly preferred, but also weak morphine agonists such as codeine and dextropropoxyphen in particular are preferred as well.

25 Advantageously, the pharmaceutical compositions according to the invention will be in the form of a unit dose.

In the pharmaceutical combination in accordance with the present invention, the weight ratio of the cyclooxygenase-2 inhibiting compound to the compound selected from acetaminophen and the opiates will be that which possesses the greater

synergy between the two combined compounds, it will be between 0.01 and 10 for the majority of the examples and will be preferably from 0.1 to 3.5.

The daily dose which can be used of the various compounds constituting the pharmaceutical combination in accordance with the present invention will of course  
5 depend upon the state of the patient to be treated.

A suitable daily dose of cyclooxygenase-2 inhibitor will generally be between about 50 mg and about 800 mg.

The pharmaceutical compositions in accordance with the present invention are suitable in the treatment of inflammatory phenomena as well as in the treatment of  
10 pain.

Their use may be cited for example in the treatment of arthritis, especially rheumatoid arthritis, spondylitis, gouty arthritis, osteoarthritis, juvenile arthritis, autoimmune diseases and lupus erythematosus.

These compositions can also be used within the context of the treatment of  
15 bronchial asthma, dysmenorrhea, tendinitis, bursitis, dermatological inflammations such as psoriasis, eczema, burns and dermatitis.

These compositions can also be used within the context of the treatment of gastrointestinal inflammations, Crohn's disease, gastritis and ulcerative colitis, in the prevention of cancer, especially adenocarcinoma of the colon, in the prevention of  
20 neurodegenerative diseases, particularly Alzheimer's disease, in the prevention of stroke and epilepsy, and in the prevention of premature labour.

Finally, these compositions can be used within the context of the treatment of pain symptoms, especially in the treatment of myalgia, articular pain or neuralgia, dental pain, herpes zoster and migraine, in the treatment of rheumatic complaints and  
25 pain of cancerous origin, and also as complementary treatments for infectious and febrile states.

The invention further covers a method of therapeutic treatment of mammals, characterized in that it consists in administering to this mammal a therapeutically

effective amount of a combination of a cyclooxygenase-2 inhibiting compound and a compound selected from acetaminophen and the opiates such as described previously.

This method especially enables treating inflammatory phenomena and pain.

5

### Description of the Drawings

Figure 1 graphically illustrates the antinociceptive effect of oral *UP-454-21-codeine* combination in the phenylbenzoquinone writhing test in mice; Dunnett's test \* and \*\* for  $p<0.05$  and  $p<0.01$  respectively, indicate a significant difference in comparison to the control group. Student's test + for  $p<0.05$  indicates a significant difference between the combination and the UP-454-21 group.  $n = 6$  per group.

Figure 2 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination in the phenylbenzoquinone writhing test in mice; Dunnett's test \*\*\* indicates a significant difference in comparison to the control group for  $p<0.001$ . Student's test  $t^{ooo}$  indicates a significant difference in comparison to the UP-454-21 group for  $p<0.001$ .  $n = 6$  per group.

Figure 3 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination in the hot plate test ( $52^{\circ}\text{C}$ ) in mice; Dunnett's test \*\* indicates a significant difference in comparison to the control group for  $p<0.01$ . Student's test  $t^{ooo}$  indicates a significant difference in comparison to the UP-454-21 group for  $p<0.001$ .  $n = 10$  per group.

Figure 4 graphically illustrates the antinociceptive effect of oral *UP-454-21-dextropropoxyphene* combination in the hot plate test ( $52^{\circ}\text{C}$ ) in mice; Dunnett's test \*\*\* indicates a significant difference in comparison to the control group for  $p<0.001$ . Student's test  $^{ooo}$  indicates a significant difference between the combination and the UP-454-21 group for  $p<0.001$ .  $n = 10$  per group.

Figure 5 graphically illustrates the antinociceptive effect of oral *UP-454-21-oxycodone* combination in the hot plate test ( $52^{\circ}\text{C}$ ) in mice; Dunnett's test \* for  $p<0.05$  indicates a significant difference in comparison to the control group.

Student's test + for p<0.05 indicates a significant difference between the combination and the UP-454-21 group. n = 10 per group.

Figure 6 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination on thermal nociceptive threshold after intraplantar injection

- 5 of complete Freund's adjuvant in rats; Dunnett's test \* for p<0.05 indicates a significant difference in comparison to the control group. n = 7 per group

Figure 7 graphically illustrates the antinociceptive effect of oral *UP-454-21-oxycodone* combination in the kaolin-induced arthritis test in rat; Dunnett's test \*\* for p<0.01 indicates a significant difference in comparison to the control group.

- 10 Student's test ++ for p<0.01 indicates a significant difference between the combination and the oxycodone group. n = 10 per group.

Figure 8 graphically illustrates the antinociceptive effect of oral *UP-454-21-paracetamol* combination on carrageenin-induced hyperalgesia in rats; Dunnett's test \*\* indicates a significant difference in comparison to the control group. n = 10 per

- 15 group.

Figure 9 graphically illustrates the antinociceptive effect of oral *UP-454-21-oxycodone* combination on carrageenin-induced hyperalgesia in rats; Dunnett's test \*, \*\* for p<0.05 and p<0.01 indicates a significant difference in comparison to the control group. n = 10 per group.

- 20 Figure 10 graphically illustrates the antinociceptive effect of oral *UP-454-21-dextropropoxyphene* combination on carrageenin-induced hyperalgesia in rats; Student's test + indicates a significant difference between the combination and the UP-454-21 group for p<0.05. n = 10 per group.

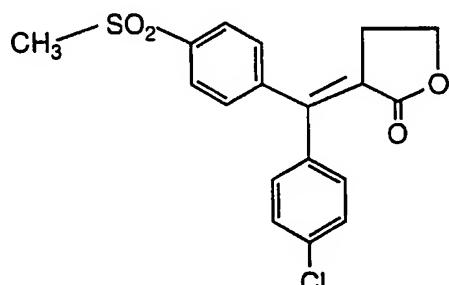
- 25 Figure 11 graphically illustrates the antinociceptive effect of oral *UP-454-21-codeine* combination on carrageenin-induced hyperalgesia in rats. Dunnett's test \* for p<0.05 indicates a significant difference in comparison to the control group.

Student's test + for p<0.05 indicates a significant difference between the combination and the codeine group. n = 10 per group.

**Demonstration of the analgesic properties of the pharmaceutical combination.**

In order to demonstrate the specific analgesic properties of the pharmaceutical combination in accordance with the present invention, several pharmacological tests have been performed whose experimental protocols and results 5 obtained will be given below.

In these tests, the compound used as an example of a selective cyclooxygenase-2 inhibitor is the compound known under the code name of UP 454-21 of the following general formula:



10

The results obtained for the first four tests are expressed in percentage inhibition of the pain reaction with respect to a control group.

15       **Test no. 1 : phenylbenzoquinone test in the mouse**

This test was carried out according to the method described by E. Siegmung,, R. Cadmus and G. Lu, A method for evaluating both non-narcotic and narcotic analgesics. Proc. Sec. Exp. Biol. Med. 1957 ; (95): 729-731.

One hour after the oral administration of the compound or the combination 20 under study, a 0.02% solution of phenylbenzoquinone (PBQ) is administered via the intra-peritoneal route in the mouse.

The number of pain reactions (abdominal torsions and stretches) is then counted between the fifth and sixth minute after the injection of phenylbenzoquinone.

The results obtained are represented in Figures I and 2 which show the potentiation effect exerted by codeine (FIG. 1) and by paracetamol (FIG. 2) on the cyclooxygenase-2 inhibiting compound (UP 454-21).

5

**Test no. 2 : Heated plate test**

The test is carried out by following the experimental protocol described by N. B. Eddy, C.F. Toucheberry and J.E. Lieberman, Synthetic analgesics. 1 -Methadone isomers and derivatives. *J. Pharmacol. Exp. Ther.* 1950 ; (98) : 121137.

10 The mouse disposed on a plate heated to 52'C ± 0.05 shows its pain by licking its front paws, or more rarely by a jump.

The reaction time is then noted down, the maximum time being 30 seconds.

The compounds or combinations studied are administered via the oral route one hour before the test.

15 The results obtained are represented in Figures 3 to 5 which clearly show the potentiation effect exerted by paracetamol (FIG. 3), by dextropropoxyphen (FIG. 4) and by oxycodone (FIG. 5) upon the cyclooxygenase-2 inhibitor (UP 454-21).

**Test no. 3 : Plantar test**

20 The test is carried out in the rat by following the experimental protocol described by R. Hargreaves, F. Brown, C. Flores and J. Joris, A new and sensitive method for measuring thermal nociception in cutaneous hyperalgesia. *Pain.* 1988 (32) : 77-88.

An inflammation is induced by intraplantar injection of a 0.05% suspension of 25 Mycobacterium butyricum. Six hours after this injection, a heat stimulus (infrared ray) is applied onto the plantar face of the hind paw of the rat.

The nociceptive reaction of the animal manifests itself by the withdrawal or the licking of the paw.

The time of appearance of the pain reaction is then noted down.

The compounds and the combination studied are administered via the oral route one hour before the plantar test.

The results obtained are represented in Figure 6 which shows the effect of potentiation exerted by paracetamol upon the cyclooxygenase-2 inhibiting compound  
5 (UP 454-21).

**Test no. 4 : Kaolin-induced arthritis test in the rat**

An inflammation is induced by the administration of a 10% aqueous kaolin suspension into the tibio-femoral joint in the rat.

10 The compounds and the combinations studied are administered orally 30 minutes after the injection of kaolin.

The spontaneous painful behavior (discomfort in walking) is then quoted 5 and 6 hours after the injection of kaolin.

15 The results obtained are represented in Figure 7 which shows the effect of potentiation exerted by oxycodone upon the cyclooxygenase-2 inhibiting compound (UP 454-21).

**Test no .5 : Paw pressure test in the carrageenin-induced hyperalgesia model**

20 The inflammation is induced in the rat by plantar administration of a 2% carrageenin solution.

Three (3) hours after this injection, an increasing pressure is exerted upon the  
25 animal's paw.

The pain threshold, expressed in grams, is then noted down.

The compounds and the combinations studied are administered orally one hour before the paw pressure test.

30 The results obtained are represented in Figures 8 to 11 which show respectively the effect of potentiation exerted by paracetamol (FIG. 8), by oxycodone

(FIG. 9), by dextropropoxyphen (FIG. 10) and by codeine (FIG. 11) upon the cyclooxygenase-2 inhibiting compound (UP 454-21).

Several examples of pharmaceutical compositions according to the invention  
5 will now be given:

**EXAMPLE I: UP 454-2 1/ACETAMINOPHEN COMBINATIONS**

**Example 1A: Capsule (size no. 0)**

10	UP 454-21.....	50 mg
	Acetaminophen.....	300 mg
	Microcrystalline cellulose.....	80 mg
	Hydroxypropyl methyl cellulose .....	10 mg
	Magnesium stearate .....	20 mg

15 for a capsule

**Example 1B: Tablet**

20	UP 454-21.....	50 mg
	Acetaminophen .....	300 mg
	Microcrystalline cellulose .....	40 mg
	Lactose .....	40 mg
	Hydroxypropyl methyl cellulose.....	10 mg
	Magnesium stearate.....	20 mg
	Hydroxypropyl cellulose.....	50 mg

25 for a tablet

**Example 1C: Suppository**

30	UP 454-21.....	100 mg
	Acetaminophen .....	600 mg
	Semi-synthetic glyceride (suppocire).....	1140 mg

for a suppository

**Example 1D: Ophthalmic solution**

35	UP 454-21 .....	0.1%
	Acetaminophen .....	1%
	Castor oil (Cremophor EL) .....	5%
	Polysorbate 80 .....	5%
	Water preparation for injection.....	q.s.p. 100%

**Example 1E : Injectable preparation**

5	UP 454-21.....0.1%
	Acetaminophen.....1%
	PEG 400.....30%
	Ethyl alcohol.....20%
	Water preparation for injection.....q.s.p. 100%

**10 EXAMPLE 2: UP 454-21/DEXTROPROPOXYPHEN COMBINATIONS****Example 2A: Capsule (size no. 1)**

15	UP 454-21 ..... 50 mg
	Dextropropoxyphen..... 20 mg
	Microcrystalline cellulose ..... 100 mg
	Hydroxypropyl methyl cellulose..... 10 mg
	Magnesium stearate..... 5 mg

for a capsule

**20 Example 2B : Tablet**

20	UP 454-21 ..... 50 mg
	Dextropropoxyphen..... 20 mg
	Microcrystalline cellulose ..... 100 mg
	Lactose ..... 100 mg
25	Hydroxypropyl methyl cellulose..... 10 mg
	Magnesium stearate..... 5 mg
	Hydroxypropyl cellulose..... 50 mg

for a tablet

**30 Example 2C : Suppository**

30	UP 454-21 1 00 mg
	Dextropropoxyphen..... 40 mg
	Semi-synthetic glyceride (suppocire) .... 1880 mg

for a suppository

**35 Example 2D : Ophthalmic solution**

35	UP 454-21.....0.1%
	Dextropropoxyphen .....0.1%
	Castor oil (Cremophor EL)..... 5%
40	Polysorbate 80 .....1%
	Water preparation for injection.....q.s.p. 100%

**Example 2E : Injectable preparation**

5            UP 454-21 ..... 0.1%  
              Dextropropoxyphen ..... 0.1%  
              PEG 400 ..... 30%  
              Ethyl alcohol ..... 10%  
              Water preparation for injection ..... q.s.p. 100%

**EXAMPLE 3: UP 454-21/CODEINE COMBINATIONS**10            **Example 3A: Capsule (size no. 1)**

15            UP 454-21 ..... 50 mg  
              Codeine ..... 20 mg  
              Microcrystalline cellulose ..... 100 mg  
              Hydroxypropyl methyl cellulose ..... 10 mg  
              Magnesium stearate ..... 5 mg  
              for a capsule

**Example 3B: Tablet**

20            UP 454-21 ..... 50 mg  
              Codeine ..... 20 mg  
              Microcrystalline cellulose ..... 100 mg  
              Lactose ..... 100 mg  
              Hydroxypropyl methyl cellulose ..... 10 mg  
              Magnesium stearate ..... 5 mg  
              Hydroxypropyl cellulose ..... 50 mg

or a tablet

**Example 3C : Suppository**

30            UP 454-21 ..... 100 mg  
              Codeine ..... 40 mg  
              Semi-synthetic glyceride (suppocire) ..... 1880 mg  
              for a suppository

**Example 3D : Ophthalmic solution**

5            UP 454-21 ..... 0 - 1 %  
               Codeine ..... 0.1%  
               Castor oil (Cremophor EL) ..... 5.%  
               Polysorbate 80 ..... 1.%  
               Water preparation for injection.....q.s.p 100 %

**Example 3E : Injectable preparation**

10            LT 454-21 ..... 0.1%  
               Codeine ..... 0.1%  
               PEG 400 ..... 30.%  
               Ethyl alcohol ..... 10%  
               Water preparation for injection.....q.s.p. 100 %

**15 EXAMPLE 4: UP 454-21/OXYCODONE COMBINATIONS****Example 4A : Capsule (size no. 1)**

20            UP 454-21..... 50 mg  
               Oxycodone ..... 15 mg  
               Microcrystalline cellulose ..... 100 mg  
               Hydroxypropyl methyl cellulose ..... 10 mg  
               Magnesium stearate ..... 5 mg

for a capsule

**Example 4B : Tablet**

25            UP 454-21..... 50 mg  
               Oxycodone ..... 15 mg  
               Microcrystalline cellulose ..... 100 mg  
               Lactose ..... 100 mg  
               Hydroxypropyl methyl cellulose ..... 10 mg  
               Magnesium stearate ..... 5 mg  
               Hydroxypropyl cellulose..... 50 mg

for a tablet

**Example 4C : Suppository**

30            UP 454-21 ..... 100 mg  
               Oxycodone ..... 30 mg  
               Semi-synthetic glyceride (suppocire)..... 1900 mg

40            for a suppository

Example 4D : Ophthalmic solution

5            UP 454-21 .....0.1%  
              Oxycodone .....0.06%  
              Castor oil (Cremophor EL) .....5%  
              Polysorbate 80 .....1%  
              Water preparation for injection.....q.s.p. 100%

Example 4E : Injectable preparation

10          UP 454-21 .....0.1%  
              Oxycodone .....0.06%  
              PEG 400 .....30%  
              Ethyl alcohol .....10%  
              Water preparation for injection.....q.s.p. 100 %

15

What is claimed is:

1. A pharmaceutical composition, which comprises as active principle, a combination of a cyclooxygenase-2 inhibitor and a compound selected from the group consisting of acetaminophen and the opiates.  
5
2. The pharmaceutical composition according to claim 1, characterised in that the cyclooxygenase-2 inhibiting compound is (Z)-3-[1-(4-chlorophenyl)-1-(4-methanesulphonylphenyl)methylene]dihydrofuran-2-one.
3. The pharmaceutical composition according to claims 1 or 2,  
10 characterised in that said opiate compound is selected from the group consisting of oxycodone, codeine and dextropropoxyphene.
4. The pharmaceutical composition according to claims 1 to 3, characterised in that it is presented in a form suitable for an administration via a route selected from the group consisting of the oral route, the parenteral route, the rectal route, the ocular route, the transdermal route, the nasal route, and the auricular route.  
15
5. The pharmaceutical composition according to claims 1 to 4, characterised in that the weight ratio of the cyclooxygenase-2 inhibiting compound to the compound selected from the group consisting of acetaminophen and the opiates is selected in order to lead to the greater synergy between the two combined compounds, the weight ratio ranges preferentially from about 0.01 to 10, and more preferentially from 0.1 to 3.5.  
20
6. The pharmaceutical composition according to claims 1 to 5, characterised in that it is presented as a unit dose containing from 50 mg to 200 mg of cyclooxygenase-2 inhibiting compound.  
25

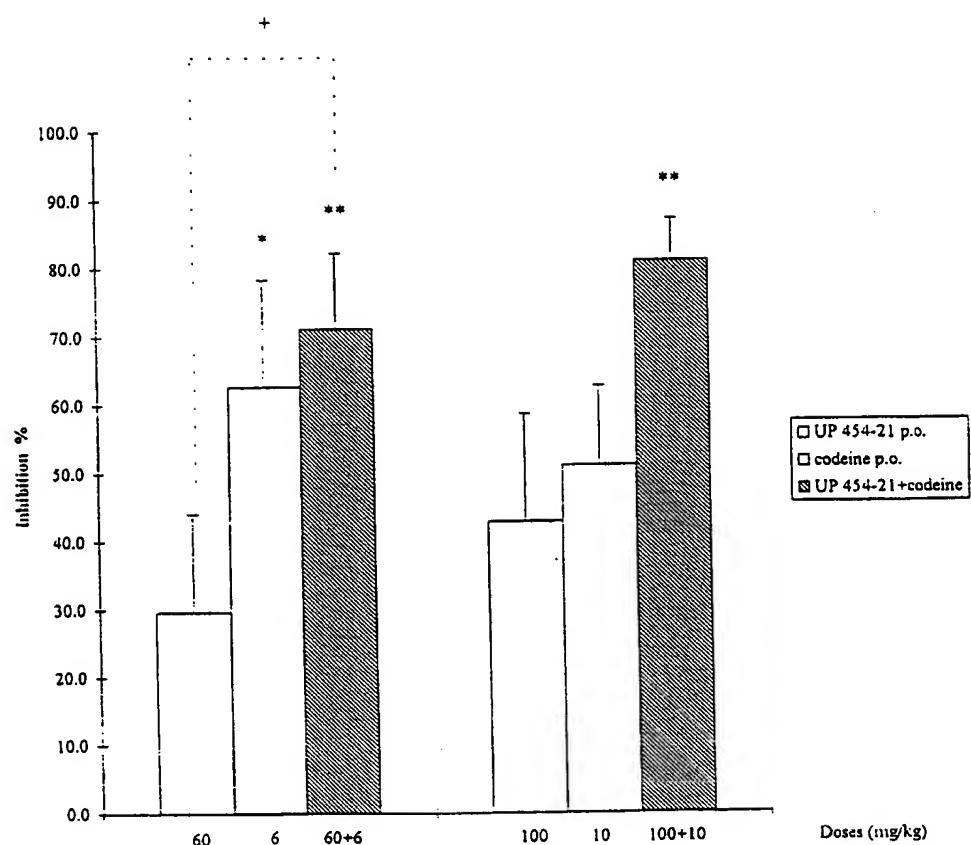


Figure 1

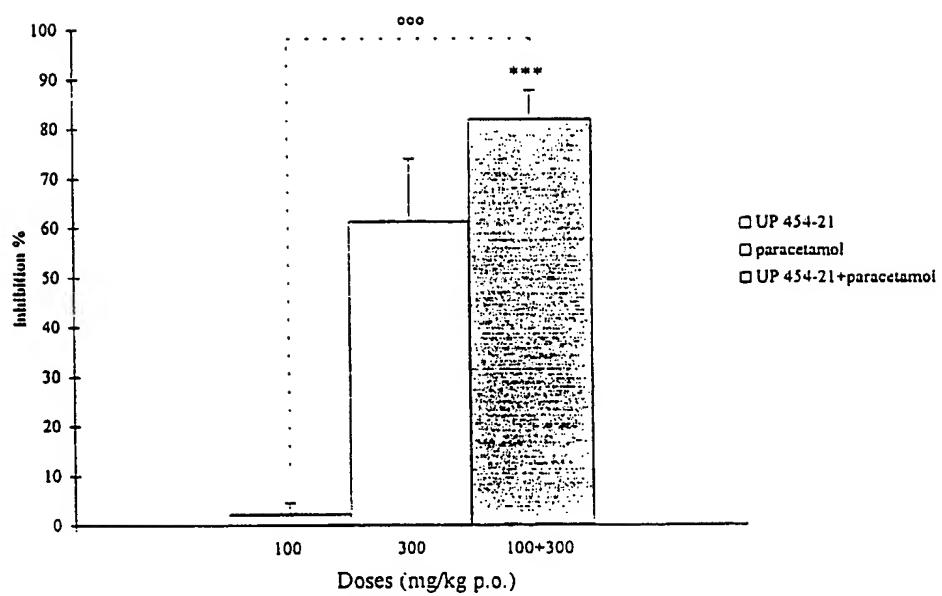


Figure 2

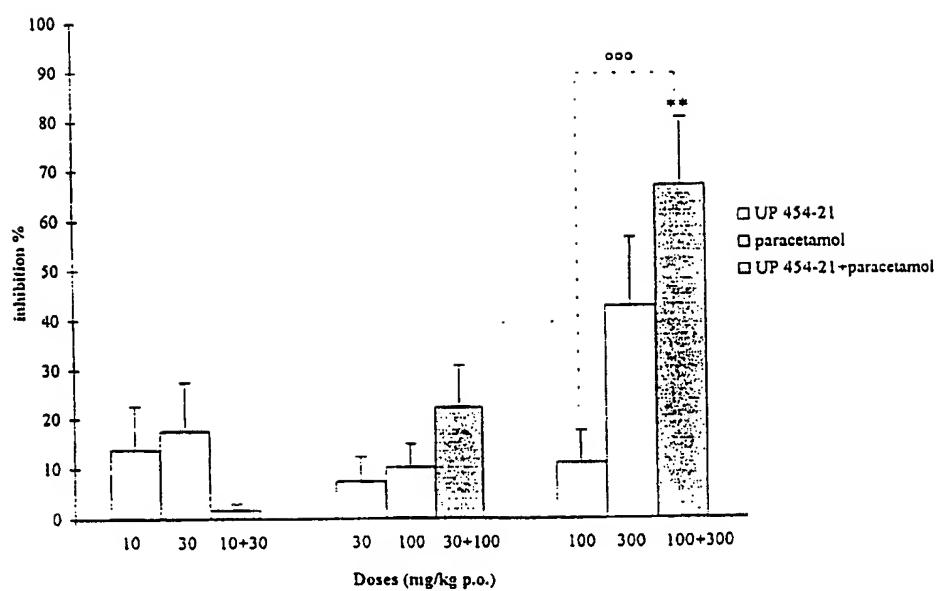


Figure 3

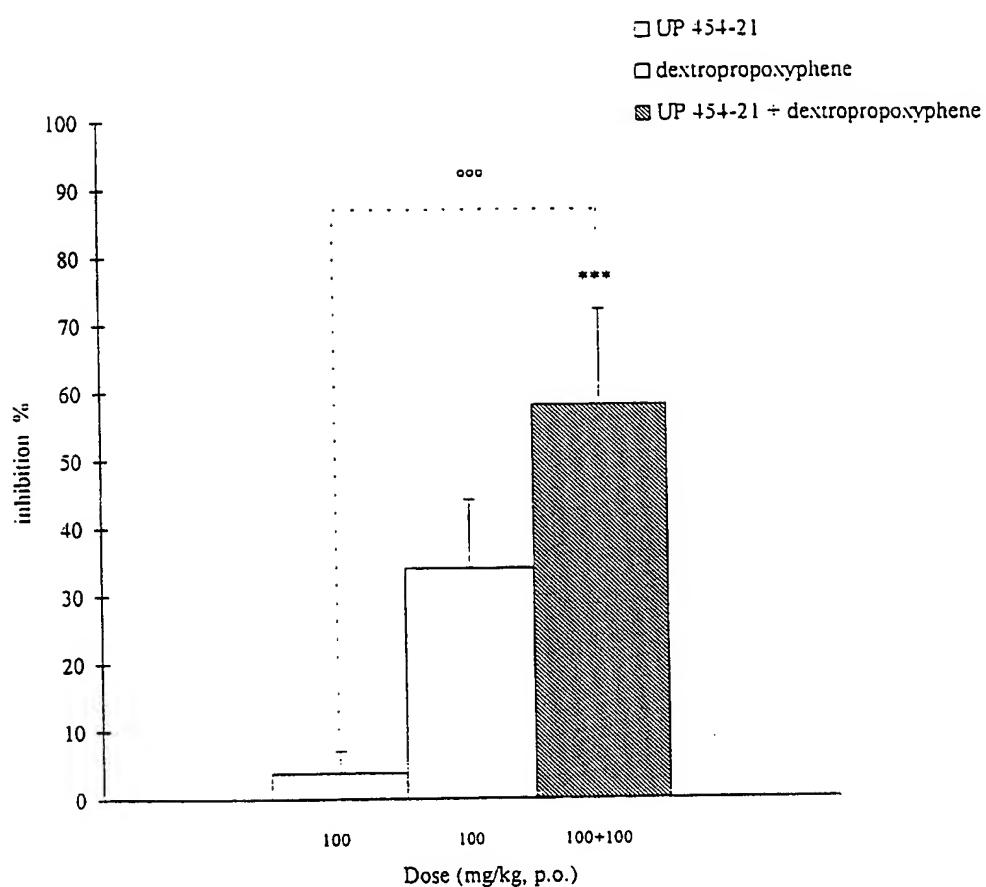


Figure 4

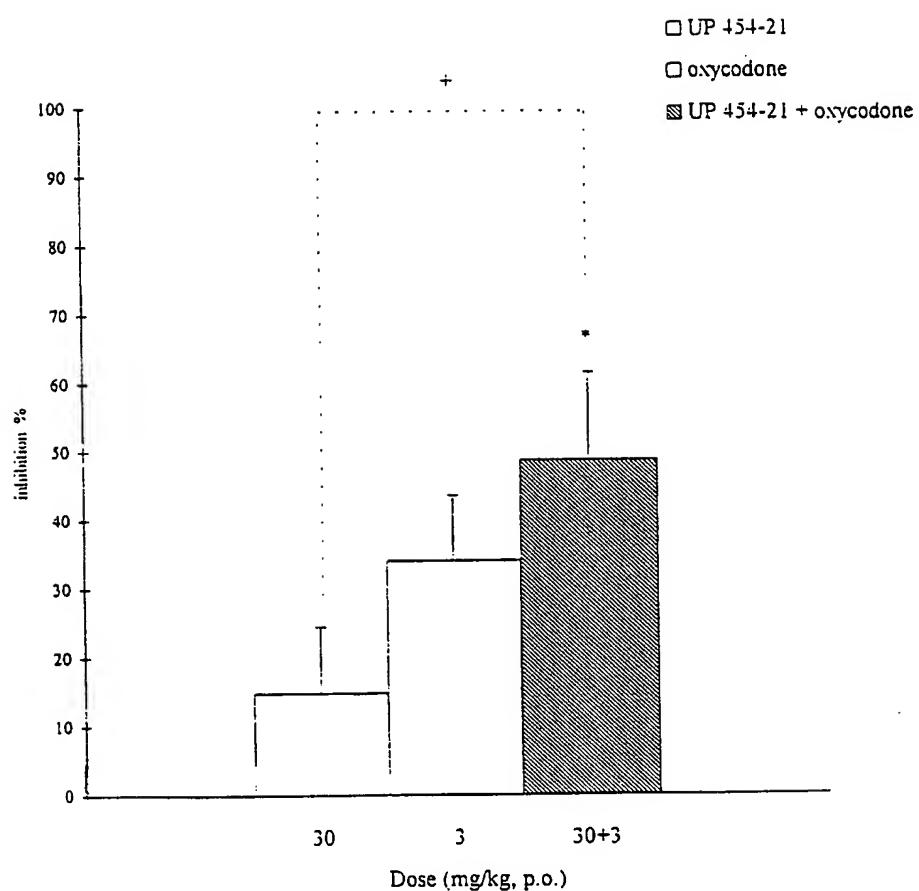


Figure 5

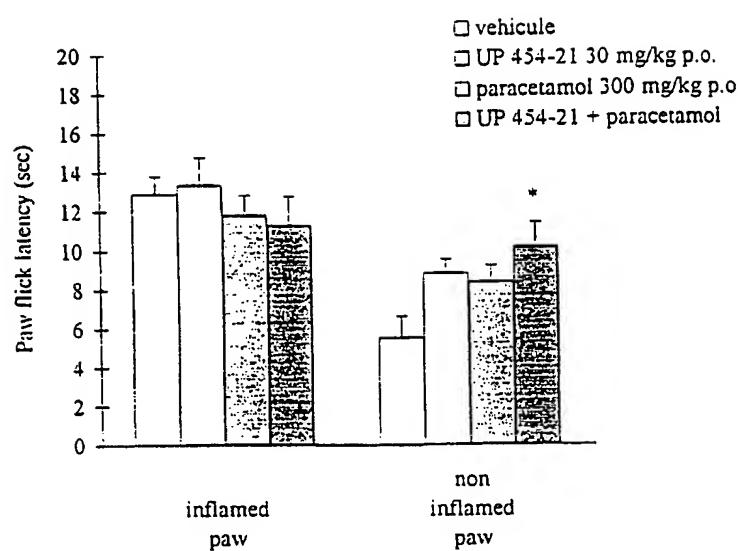


Figure 6

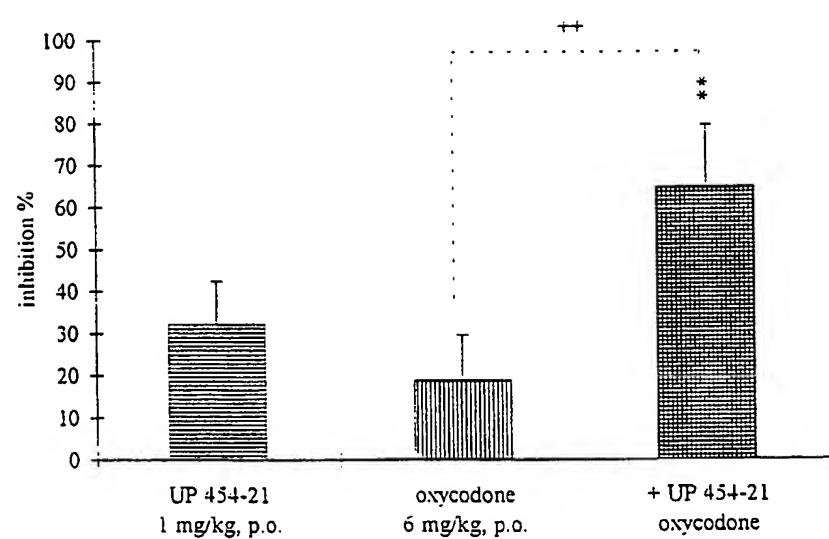


Figure 7

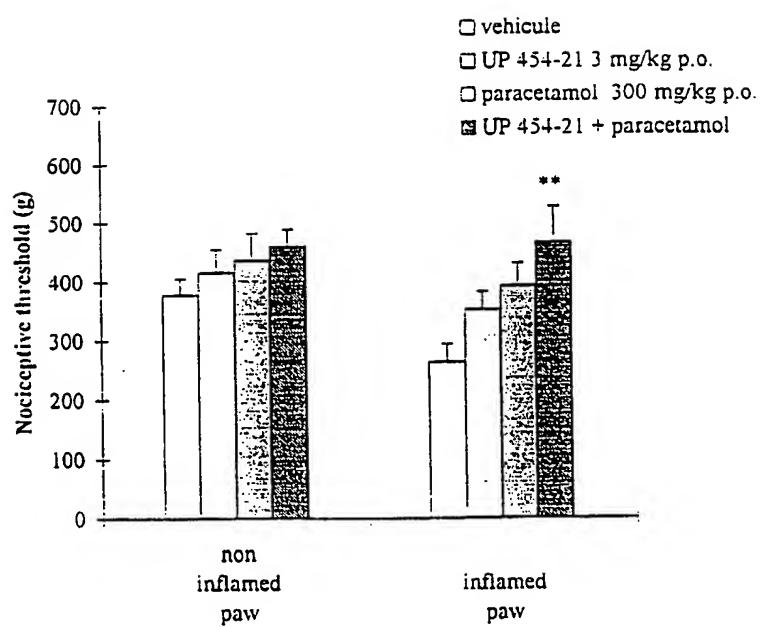


Figure 8

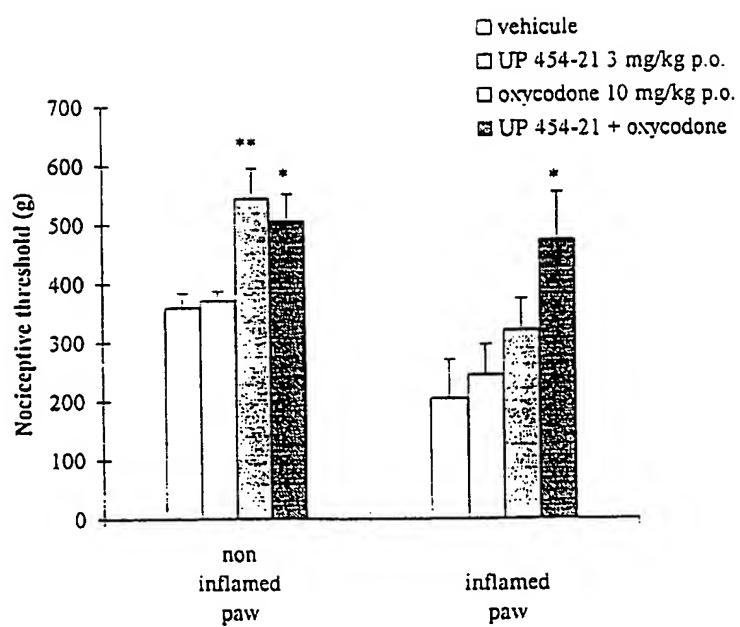


Figure 9

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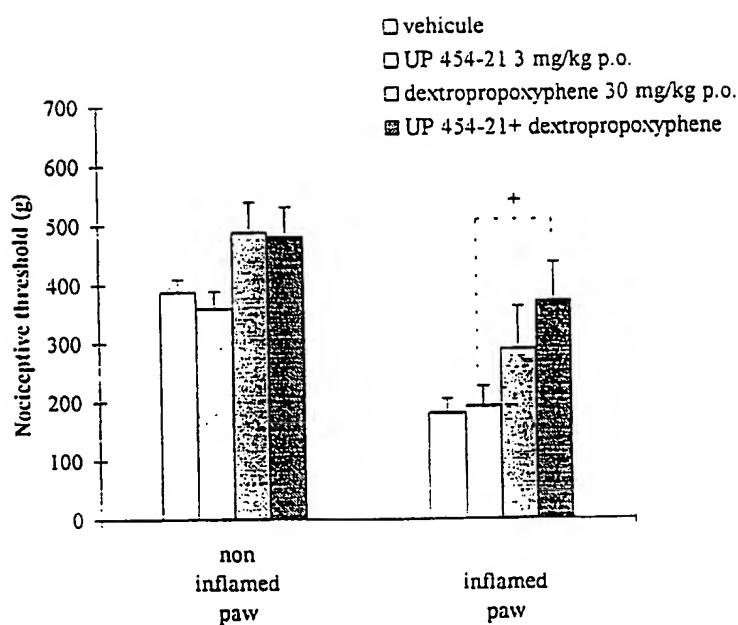


Figure 10

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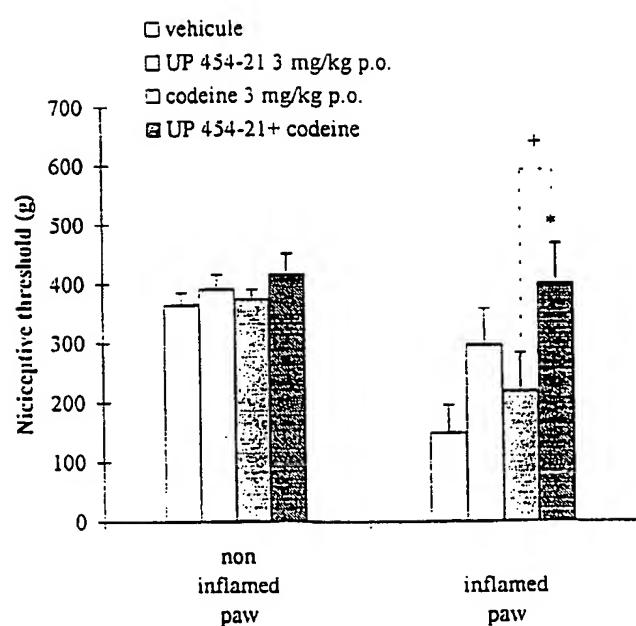


Figure 11

## INTERNATIONAL SEARCH REPORT

International Application No PCT/IB 98/01789
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A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K45/06
--------------------------------------------------------

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
--------------------

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT
----------------------------------------

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 19469 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); GRIMM ERICH (CA); LEG) 27 June 1996 see abstract see page 22, line 33 - page 23, line 18 ---	1,3,4
X	WO 96 36623 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); GRIMM ERICH (CA); WAN) 21 November 1996 see abstract see page 21, line 7 - line 26 ---	1,3,4
X	US 5 552 422 A (GAUTHIER JACQUES Y ET AL) 3 September 1996 see column 9, line 25 - column 10, line 14 ---	1,3,4 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

25 March 1999

Date of mailing of the international search report

01/04/1999

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Leherte, C

## INTERNATIONAL SEARCH REPORT

International Application No PCT/IB 98/01789
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 521 213 A (PRASIT PETPIBOON ET AL) 28 May 1996 see column 5, line 56 - column 6, line 22 ----	1,3,4
X	WO 96 31509 A (GLAXO GROUP LTD ;BESWICK PAUL JOHN (GB); CAMPBELL IAN BAXTER (GB);) 10 October 1996 see page 5, line 13 - page 7, line 32 ----	1,3,4
X	WO 97 14691 A (MERCK FROSST CANADA INC ;BELLEY MICHEL (CA); GAUTHIER JACQUES Y (C) 24 April 1997 see page 42, line 11 - page 43, line 7 -----	1,3,4

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/IB 98/01789

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9619469	A 27-06-1996	AU 702591 B AU 4294196 A CA 2206978 A EP 0799218 A JP 10511089 T		25-02-1999 10-07-1996 27-06-1996 08-10-1997 27-10-1998
WO 9636623	A 21-11-1996	US 5691374 A AU 5642496 A CA 2219129 A EP 0828724 A		25-11-1997 29-11-1996 21-11-1996 18-03-1998
US 5552422	A 03-09-1996	AU 697650 B AU 4381496 A CA 2209895 A WO 9621667 A EP 0802917 A JP 11501902 T		15-10-1998 31-07-1996 18-07-1996 18-07-1996 29-10-1997 16-02-1999
US 5521213	A 28-05-1996	AU 689302 B AU 3249295 A CA 2197895 A WO 9606840 A EP 0778834 A JP 10504829 T		26-03-1998 22-03-1996 07-03-1996 07-03-1996 18-06-1997 12-05-1998
WO 9631509	A 10-10-1996	AU 5276696 A BR 9604870 A CA 2216809 A CN 1186492 A CZ 9703133 A EP 0819127 A HU 9801602 A JP 11501049 T NO 974595 A NZ 304886 A PL 322623 A SK 133297 A		23-10-1996 26-05-1998 10-10-1996 01-07-1998 18-03-1998 21-01-1998 30-11-1998 26-01-1999 03-12-1997 25-11-1998 02-02-1998 08-07-1998
WO 9714691	A 24-04-1997	AU 7123696 A CA 2233178 A CN 1200119 A CZ 9801101 A EP 0863891 A HR 960458 A JP 11500146 T NO 981628 A PL 326203 A		07-05-1997 24-04-1997 25-11-1998 16-09-1998 16-09-1998 30-04-1998 06-01-1999 27-05-1998 31-08-1998